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(54) Title: METHOD OF PREVENTING ANDROGENETIC ALOPECIA WITH 5-ALPHA REDUCTASE INHIBITORS

(57) Abstract

The instant invention involves a method of preventing androgenetic alopecia and promoting hair growth, by administering to a patient in need of such treatment, particularly individuals predisposed to androgenetic alopecia, including men with normal androgen levels who have a genetic predisposition to develop androgenetic alopecia, a hair maintaining amount of a 5α-reductase 2 inhibitor, such as finasteride.

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TITLE OF THE INVENTION

METHOD OF PREVENTING ANDROGENETIC ALOPECIA WITH 5-ALPHA REDUCTASE INHIBITORS

The present invention is concerned with the prevention of androgenetic alopecia, including male pattern baldness, with compounds that are 5-alpha reductase isozyme 2 inhibitors.

BACKGROUND OF THE INVENTION

Certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, androgenetic alopecia (also called androgenic alopecia) which includes female and male pattern baldness, and benign prostatic hyperplasia, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone ("T") or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., *Endocrinol.* **1972**, *91* (2). However, these products, though devoid of hormonal effects, compete with all natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host and/or initiate feed-back effects which would cause hyperstimulation of the testes.

The principal mediator of androgenic activity in some target organs, e.g. the prostate, is 5α-dihydrotestosterone ("DHT"), formed locally in the target organ by the action of testosterone-5α-reductase. Inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation in these organs. See especially United States Patent No. 4,377,584 assigned to Merck & Co., Inc., issued March 22, 1983. It is now known that a second 5α-reductase isozyme exists, which interacts with skin tissues, especially in

scalp tissues. See, e.g., G. Harris, et al., Proc. Natl. Acad. Sci. USA, Vol. 89, pp. 10787-10791 (Nov. 1992). The isozyme that principally interacts in skin tissues is conventionally designated as 5α-reductase 1 (or 5α-reductase type 1), while the isozyme that principally interacts within the prostatic tissues is designated as 5α-reductase 2 (or 5α-reductase type 2).

Finasteride (17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one), which is marketed by Merck & Co., Inc. under the tradename PROSCAR®, is an inhibitor of 5α-reductase 2 and is known to be useful for the treatment of hyperandrogenic conditions. See e.g., U.S. Patent No. 4,760,071. Finasteride is currently marketed in the United States and worldwide for the treatment of benign prostatic hyperplasia. Finasteride's utility in the treatment of androgenetic alopecia and prostatic carcinoma is also disclosed in the following documents: EP 0 285,382, published 5 October 1988; EP 0 285 383, published 5 October 1988; Canadian Patent no. 1,302,277; and Canadian Patent no. 1,302,276. The specific dosages exemplified in the above-noted disclosures varied from 5 to 2000 mg per patient per day.

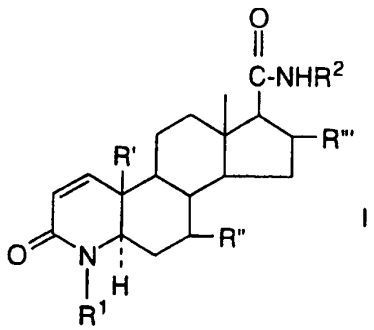
In the prevention of androgenetic alopecia, which includes both female and male pattern baldness, and other hyperandrogenic conditions, it would be desirable to administer the lowest dosage possible of a pharmaceutical compound to a patient and still prevent the condition. Applicants have surprisingly and unexpectedly discovered that a 5α-reductase 2 inhibitor is particularly useful in the prevention of androgenetic alopecia in individuals predisposed to androgenetic alopecia. These individuals include men with normal androgen levels who have a genetic predisposition to develop androgenetic alopecia. These men may be identified as those with a family history of early and aggressive onset of baldness in a sibling, parent or grandparent.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention involves a method of preventing androgenetic alopecia and promoting hair growth, which comprises administering to a patient in need of such treatment a 5α-reductase 2 inhibitor. The term "prevention" includes reducing the risk of

developing androgenetic alopecia, particularly in individuals predisposed to androgenetic alopecia. These individuals include men with normal androgen levels who have a genetic predisposition to develop androgenetic alopecia. These men may be identified as those with a family history of early and aggressive onset of baldness in a sibling, parent or grandparent. The "prevention" of androgenetic alopecia is further defined in a patient in a clinical setting when a patient does not lose hair below the baseline amount of hair the patient had when the 5α-reductase 2 inhibitor is first administered, as determined by any of the following techniques: hair count, investigator assessment, or global photography, or a combination of these techniques. In addition to the prevention of the development of baldness, the method of the present invention may also be employed to prevent further hair loss. The term androgenetic alopecia includes both male pattern baldness, and female pattern baldness, the latter of which is characterized by a more diffuse balding pattern. In one embodiment of this invention, the 5α-reductase 2 inhibitor is administered in a dosage amount of from 0.01 to 100 mg/day. In one class of this embodiment, the 5α-reductase 2 inhibitor is administered in a dosage amount of from 0.05 to 10 mg/day, and in a sub-class of this embodiment, the 5α-reductase 2 inhibitor is administered in dosage amounts of about 0.2 to 5 mg/day. Illustrating this subclass are dosage amounts of about 0.2, 1.0, and 5.0 mg/day. Compounds which are inhibitors of 5α-reductase 2 can be determined by employing the assay described below in Example 3.

In a second embodiment of this invention, the method of preventing androgenetic alopecia comprises administration of 5α-reductase 2 inhibitor compounds which have the structural formula I



I

or a pharmaceutically acceptable salt thereof wherein:

R^1 is selected from hydrogen, methyl and ethyl;

R^2 is a hydrocarbon radical selected from straight and branched chain alkyl of from 1-12 carbons or monocyclic aryl optionally containing one to three substituents selected from: lower alkyl of from 1-2 carbon atoms; halogen-substituted C_{1-2} alkyl, and halogen;

R' is hydrogen or methyl;

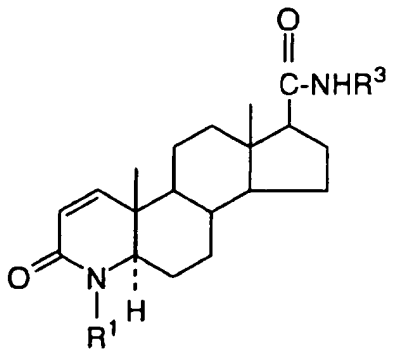
R" is hydrogen or β-methyl; and

R"' is hydrogen, α-methyl or β-methyl.

It is understood in the description above that an alkyl substituent of two or fewer carbons must be straight chain, but that an alkyl substituent of three or greater carbon atoms may be either straight or branched chain.

Aryl is selected from phenyl, naphthyl, thiophene, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, pyrrole, benzofuran, furan, indole, purine, and the like, but is preferably monocyclic aryl, and most preferably phenyl.

In one class of this second embodiment, the 5α-reductase 2 inhibitor compounds have the structural formula II



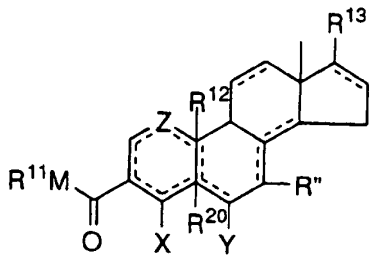
II

or a pharmaceutically acceptable salt thereof wherein:
R^1 is hydrogen, or methyl; and
R^3 is branched chain alkyl of from 4-8 carbons.

Representative compounds that may be employed in the present invention include the following:
17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-isobutylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-tert-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-neopentylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-tert-amylcarbamoyl-4-aza-5α-androst-1-en-3-one,
17β-(N-2,5-bis(trifluoromethyl)phenylcarbamoyl)-4-aza-5α-androst-1-en-3-one, and
17β-(N-tert-hexylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
and the corresponding compounds wherein the 4-nitrogen is substituted in each of the above named compounds by a methyl or an ethyl radical.

Also included as representative compounds are any of the above indicated compounds having the N-branched chain alkyl substituent replaced by a methyl, ethyl, propyl, i-propyl, butyl, phenyl: 2, 3 or 4 tolyl, xylyl, 2-bromo or 2-chlorophenyl, 2-6-dichloro, or a 2,6-dibromophenyl substituent.

In a third embodiment of this invention, the method of preventing androgenetic alopecia comprises administration of 5α-reductase 2 inhibitor compounds which have the structural formula III:



III

wherein:

The A ring has up to 2 double bonds;

The B, C, and D rings have optional double bonds where indicated by the broken lines, provided that the A-B rings and B-C rings do not have adjacent double bonds and the D ring does not have a C_{16}-C_{17} double bond when R^{13} represents two substituents or a divalent substituent;

M is O or S;

Z is CH_2 or, when part of a double bond, CH;

X is H, Cl, F, Br, I, CF_3, or C_{1-6} alkyl;

Y is H, CF_3, F, or Cl, CH_3 provided that Y is H when there is no C_5-C_6 double bond;

R^{11} is H or C_{1-8}alkyl;

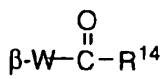
R^{12} is absent or present as H or CH_3 provided R^{12} is absent when the carbon to which it is attached is double bonded;

R^{20} is absent when there is a C_4-C_5, C_5-C_6, or C_5-C_{10}, double bond, or present as an alpha hydrogen, and

R^{13} is:

(1) α-hydrogen, α-hydroxyl or α-acetoxy and/or

(a)



where W is a bond or C_{1-12}alkyl, and R^{14} is:

(i) hydrogen,

(ii) hydroxyl,

(iii) C_{1-8}alkyl,

(iv) hydroxy C_{1-8}alkyl,
(v) C_{1-8}alkoxy,
(vi) $NR^{15}R^{16}$, where R^{15} and R^{16} are each independently selected from hydrogen, C_{1-8}alkyl, C_{3-6} cycloalkyl, phenyl; or R^{15} and R^{16} taken together with the nitrogen to which they are attached represent a 5-6 membered saturated ring comprising up to one other heteroatom selected from oxygen and nitrogen, or
(vii) OR^{17}, where R^{17} is hydrogen, alkali metal, C_{1-18}alkyl, benzyl, or

(b) β-Alk-OR^{18}, where Alk is C_{1-12} alkyl, and R^{18} is
(i) phenyl C_{1-6}alkylcarbonyl,
(ii) C_{5-10}cycloalkylcarbonyl,
(iii) benzoyl,
(iv) C_{1-8}alkoxycarbonyl,
(v) aminocarbonyl, or C_{1-8}alkyl substituted aminocarbonyl,
(vi) hydrogen, or
(vii) C_{1-8}alkyl,

(2) =CH-W-CO-R^{14} or =CH-W-OR^{18}, where W is a bond or C_{1-12} alkyl and R^{14} and R^{18} have the same meaning above, and R^{18} is also hydrogen or C_{1-20}alkylcarbonyl

(3)

where the dashed bond replaces the 17-α-hydrogen,

(4) α-hydrogen and β-$NHCOR^{19}$ where R^{19} is C_{1-12}alkyl or β-$NR^{15}R^{16}$ where R^{15} and R^{16} have the same meaning as above,

(5) α-hydrogen and β-cyano,

(6) α-hydrogen and β-tetrazolyl, or

(7) keto;

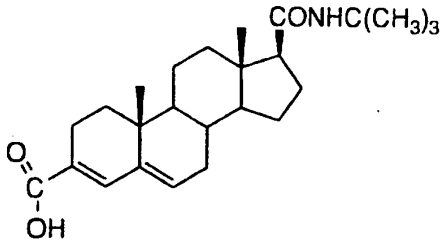
or a pharmaceutically acceptable salt thereof; except compounds in which:

The A ring has a C3-C4 double bond, the B ring has a C5-C6 double bond, R^{11} is methyl and R^{13} is keto;

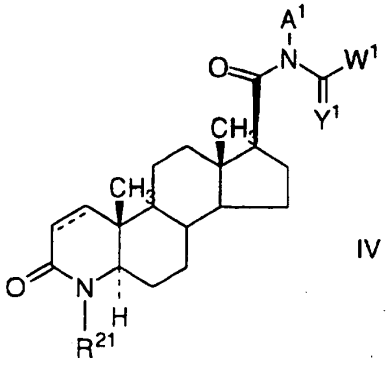
The A ring has a C3-C4 double bond, the B ring has a C5-C6 double bond, R^{11} is methyl and R^{13} is $COOCH_3$; and

The B ring has a C5-C6 double bond, R^{11} is methyl and R^{13} is $COCH_3$.

One example of a compound of this embodiment is:



In a fourth embodiment of this invention, the method of preventing androgenetic alopecia comprises administration of a 5α-reductase 2 inhibitor compound which has the structural formula IV:

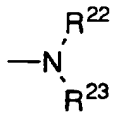


IV

wherein:

R^{21} is hydrogen, a C_{1-6}alkyl group, a benzyl group, a p-methoxybenzyl group, or a benzoyl group;

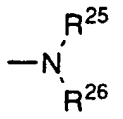
Y^1 is oxygen or sulphur;
W^1 is a group



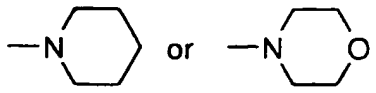
wherein each of R^{22} and R^{23} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{5-6}cycloalkyl, C_{6-9}cycloalkylalkyl and phenyl, wherein each of the groups alkyl, cycloalkyl, cycloalkylalkyl, and phenyl may be unsubstituted or substituted with a substituent $-OR^{24}$ where R^{24} is hydrogen or C_{1-4}alkyl;

A^1 is hydrogen, C_{1-6}alkyl, C_{5-6}cycloalkyl, or C_{6-9}cycloalkylalkyl wherein each of the groups alkyl, cycloalkyl, and cycloalkylalkyl, may be unsubstituted or substituted with a substituent chosen from:

(a) $-OR^{24}$ wherein R^{24} is defined above, and



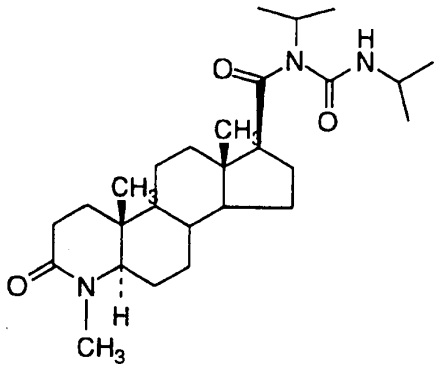
wherein either each of R^{25} and R^{26} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{5-6}cycloalkyl, and phenyl, or R^{25} and R^{26}, taken together with the nitrogen atom to which they are linked, are



and

the dotted line represents a single or double bond,
and the pharmaceutically acceptable salts thereof.

One example of a compound of this embodiment is:



or a pharmaceutically acceptable salt thereof.

The compounds of formula I and II described above can be synthesized according to procedures well known in the art, and which are described, for example, in U.S. Patent No. 4,760,071, EP 0 285,382 and EP 0 285 383. The compound finasteride is currently available as a prescription pharmaceutical from Merck & Co. Inc. The synthesis of finasteride is described in US Patent 4,760,071. A further synthesis of finasteride is described in Synthetic Communications, 30 (17), p. 2683-2690 (1990).

The compounds of formula III described above can be synthesized according to procedures well known in the art, and which are described, for example, in U.S. Patent 5,017,568.

The compound of formula IV described above can be synthesized according to procedures well known in the art, and which are described, for example, in U.S. Patents 5,155,107 and 5,342,948.

The present invention has the objective of providing methods of preventing the hyperandrogenic conditions of androgenetic alopecia, including male pattern baldness and female pattern baldness, by systemic, including oral, parenteral and topical administration of a 5α-reductase 2 inhibitor in a dosage amount 0.01 to 100 mg/day, and particularly, from about 0.05 to 10 mg/day, and more particularly 0.2 to 5 mg/day. The invention is further illustrated by dosages of about 0.2, 1.0, and 5.0 mg/day. Also, a 5α-reductase 2 inhibitor, e.g.

finasteride can be used in combination with a potassium channel opener, such as minoxidil or a pharmaceutically acceptable salt thereof, for the treatment of androgenetic alopecia, including male pattern baldness The 5α-reductase 2 inhibitor and the potassium channel opener may both be applied topically, or each agent can be given via different administration routes; for example, the 5α-reductase 2 inhibitor may be administered orally while the potassium channel opener may be administered topically.

The present invention also has the objective of providing suitable systemic, including oral, parenteral and topical pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing 5α-reductase 2 inhibitor compounds as the active ingredient for use in the treatment of the above-noted hyperandrogenic conditions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. For oral administration, for example, the compositions can be provided in the form of scored or unscored tablets containing 0.01, 0.05, 0.1, 0.2, 1.0, and 5.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

For the prevention of androgenetic alopecia including male pattern baldness, the 5α-reductase 2 inhibitor compounds may be administered in a pharmaceutical composition comprising the active compound in combination with a pharmaceutically acceptable carrier adapted for topical administration. Topical pharmaceutical compositions may be, e.g., in the form of a solution, cream, ointment, gel, lotion, shampoo or aerosol formulation adapted for application to the skin. Topical pharmaceutical compositions useful in the method of

treatment of the present invention may include about 0.001% to 0.1% of the active compound in admixture with a pharmaceutically acceptable carrier.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

In the methods of the present invention, the 5α-reductase 2 inhibitor compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs,

syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Capsules containing the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers,

cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations. See, e.g., EP 0 285 382.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The following examples illustrate the present invention and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1

Finasteride is known to occur in two distinct polymorphic crystal forms, termed "form 1" and "form II". Form I is the marketed form of finasteride as a 5 mg tablet (PROSCAR®).

Finasteride Form I can be prepared by dissolving finasteride in glacial acetic acid (ca. 100 mg/mL) and adding water with stirring until the weight % of water equals or exceeds 84%. The resulting solid phase is collected by filtration and dried under vacuum and at about 50°C. The resulting Form I is characterized by a differential scanning calorimetry (DSC) curve, at heating rate of

20°C/min and in a closed cup, exhibiting a minor endotherm with a peak temperature of about 232°C, an extrapolated onset temperature of about 223°C with an associated heat of about 11 joules/gm and by a major melting endotherm with a peak temperature of about of 261°C, an extrapolated onset temperature of about 258°C with an associated heat of about 89 J/gm. The x- ray powder diffraction pattern is characterized by d-spacings of 6.44, 5.69, 5.36, 4.89, 4.55, 4.31, 3.85, 3.59 and 3.14 . The FT-IR spectrum shows bands at 3431, 3237, 1692, 1666, 1602 and 688 cm-1. The solubilities in water and cyclohexane at 25°C are 0.05 ± 0.02 and 0.27 ± 0.05 mg/gm respectively. In addition, Form I of finasteride can be prepared by recrystallization from dry (H_2O <1mg/mL) ethyl acetate and isopropyl acetate. The isolated solids are dried under vacuum at about 50°C and have the same physical characterization data as given above.

EXAMPLE 2

Form II of finasteride can be prepared by dissolving finasteride in glacial acetic acid (ca. 100 mg/mL) and adding water with stirring until the weight % of water equals about 75% but not in excess of 80%. The resulting solid phase is collected by filtration and dried under vacuum and at about 100°C. The resulting Form II is characterized by a DSC curve, at heating rate of 20°C/min and in a closed cup, exhibiting a single melting endotherm with a peak temperature of about of 261°C, an extrapolated onset temperature of about 258°C with an associated heat of about 89 J/gm. The x- ray powder diffraction pattern is characterized by d-spacings of 14.09, 10.36, 7.92, 7.18, 6.40, 5.93, 5.66, 5.31, 4.68, 3.90, 3.60 and 3.25. The FT-IR spectrum shows bands at 3441, 3215, 1678, 1654, 1597, 1476 and 752 cm-1. The solubilities in water and cyclohexane at 25°C are 0.16+0.02 and 0.42+0.05 mg/gm respectively. In addition, Form II of finasteride can be prepared by recrystallization from ethyl acetate containing between 2 to 30 mg/mL of water and isopropyl acetate containing between 2 to 15 mg/mL of water. The isolated solids are dried under vacuum at about 80°C and have the same physical

characterization data as given above. Form II can also be prepared by heating Form I up to about 150°C, holding for about one hour and cooling back to room temperature. The Form II prepared in this manner has the same physical characterization data as given above.

EXAMPLE 3

Preparation of Human prostatic 5α-reductase.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethyl-sulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay

The reaction mixture for the type 2 5α-reductase contained 40 mM sodium citrate, pH 5.5, 0.3 μM [7-^{3}H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μl. Typically, the assay was initiated by the addition of 50-100 μg prostatic homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 μl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 μg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 mL/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757

variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate preparation were T, DHT and androstanediol.

Inhibition studies

Compounds were dissolved in 100% ethanol. IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity to 50% of the control. IC_{50} values were determined using a 6 point titration where the concentration of the inhibitor was varied from 0.1 to 1000 nM.

EXAMPLE 4

MACROPHOTOGRAPHY AND GLOBAL PHOTOGRAPHY PROCEDURE FOR DETECTION OF HAIR GROWTH

A. Macrophotographic Procedure

Location: ID card
Haircount target area

Equipment: Film: Kodak-T-max 24 exposure each of same emulsion lot number
Camera: Nikon N-6000
Lens: Nikkor 60 mm f2.8
Flashes: Nikon SB-21B Macroflash
Device: registration device

Photographic Procedure:

In these clinical photographs, the only variable allowed is the haircount. Film emulsion, lighting, framing, exposure, and reproduction ratios are held constant.

1. The haircount area on the patient is prepared as follows:

A small (~1mm) dot tattoo is placed at the beginning of the study at the leading edge of the bald area directly anterior to the center of the vertex bald spot, using a commercial tattooing machine or manually (needle and ink). An area approximately one square inch in size, centered at the tattoo at the leading edge of the balding area, is clipped short (~2mm). Cut hairs are removed from the area to be photographed, using tape. Compressed air and/or ethanol wipes may also be used to facilitate removal of cut hairs.

2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:1.2.
Aperture: Every photograph is taken at f/22.
Film: T-Max 100 (24 exposure) is used.

3. Patient's haircount target area. Three exposures (-2/3, 0, and +2/3 f-stop).

A trained technician places a transparency over the photographic print and, using a felt tip pen, places a black dot over each visible hair. The dot map transparency is then counted using image analysis with computer assistance.

Photographs are coded with a random number corresponding to study site, visit number and patient allocation number to insure blinding to time. At Month 6, baseline and Month 6 photographs are counted and data analyzed for interim analysis. At Month 12, baseline, Month 6 and Month 12 photographs are counted and data analyzed for the primary endpoint.

Methodology for detection of hair growth is also described in Olsen, E.A. and DeLong, E., J. American Academy of Dermatology, Vol. 23, p. 470 (1990).

B. Global Photographic Procedure

Locations: Color card/patient Id

Global photograph

Equipment: Film: Kodachrome KR-64 24 exposure each of same emulsion lot number

Camera: Nikon N-6000

Lens: Nikkor 60 mm f2.8

Flashes: Nikon SB-23

Photographic Procedure

In these clinical photographs, the only variable allowed is the global area's appearance. Anything extraneous to the area (clothing, furniture, walls, etc.) is eliminated from the fields to be photographed.

1. Patients will have global photographs taken prior to hair clipping with the head in a fixed position (determined by the supplied stereotactic device). Hair on the patient's head is positioned consistently so as to not obscure the bald area.

2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:6.
   Aperture: Every photograph will be taken at f/11.
   Film: Kodachrome (24 exposure) is used.

3. Patient's global photographs. Three exposures at zero compensation.

Using the above-described methodology, it can be shown that administration of 5α-reductase 2 inhibitors, including finasteride, in dosages between 0.01 and 100 mg/day per patient, for example, 5 mg/day, 1 mg/day or 0.2 mg/day, are useful in the prevention of androgenetic alopecia, and promote hair growth in patients particularly in individuals predisposed to androgenetic alopecia.

WHAT IS CLAIMED IS:

1. A method of preventing androgenetic alopecia comprising administering to a person in need of such treatment a hair maintaining amount of a 5α-reductase 2 inhibitor.

2. The method of Claim 1 wherein the dosage amount is from about 0.01 to 100.0 mg/day.

3. The method of Claim 1 wherein the dosage amount is from about 0.05 to 10.0 mg/day.

4. The method of Claim 1 wherein the dosage amount is from about 0.2 to 5.0 mg/day.

5. The method of Claim 1 wherein the dosage amount is about 0.2 mg/day.

6. The method of Claim 1 wherein the dosage amount is about 1.0 mg/day.

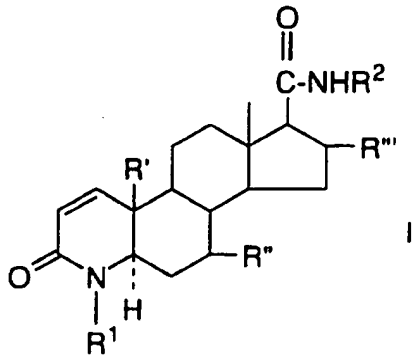
7. The method of Claim 1 wherein the dosage amount is about 5.0 mg/day.

8. The method of Claim 1 wherein the androgenetic alopecia is male pattern baldness.

9. The method of Claim 1 wherein the 5α-reductase 2 inhibitor is administered orally.

10. The method of Claim 1 wherein the 5α-reductase 2 inhibitor is administered topically.

11. The method of Claim 1 wherein the 5α-reductase 2 inhibitor has the structural formula I



I

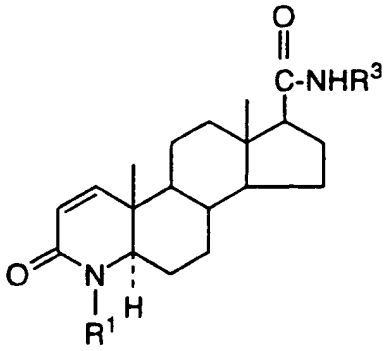
or a pharmaceutically acceptable salt thereof wherein:
R^1 is hydrogen, methyl or ethyl;
R^2 is a hydrocarbon radical selected from:

(a) straight and branched chain C_{1-12} alkyl, and

(b) monocyclic aryl unsubstituted or substituted with one to three substituents independently selected from:
C_{1-2} alkyl,
halo-substituted C_{1-2}alkyl, and
halogen (Cl, F or Br);

R' is selected from hydrogen and methyl;
R'' is selected from hydrogen and β-methyl; and
R''' is selected from hydrogen, α-methyl, and β-methyl.

12. The method of Claim 1 wherein the 5α-reductase 2 inhibitor has the structural formula II



II

or a pharmaceutically acceptable salt thereof wherein
R1 is hydrogen, or methyl; and
R3 is branched chain alkyl of from 4-8 carbons.

13. The method of Claim 1 wherein the 5α-reductase 2 inhibitor is selected from:
17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-isobutylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-tert-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-5-α-androst-1-en-3-one,
17β-(N-neopentylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-tert-amylcarbamoyl-4-aza-5α-androst-1-en-3-one,
17β-(N-2,5-bis(trifluoromethyl)phenylcarbamoyl)-4-aza-5α-androst-1-en-3-one, and
17β-(N-tert-hexylcarbamoyl)-4-aza-5α-androst-1-en-3-one.

14. A method of preventing androgenetic alopecia comprising administering to a person in need of such treatment a hair-maintaining amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.

15. The method of Claim 14 wherein the androgenetic alopecia is male pattern baldness.

16. The method of Claim 14 wherein the dosage amount is from about 0.01 to 100.0 mg/day.

17. The method of Claim 14 wherein the dosage amount is from about 0.05 to 10.0 mg/day.

18. The method of Claim 14 wherein the dosage amount is from about 0.2 to 5.0 mg/day.

19. The method of Claim 14 wherein the dosage amount is 0.2 mg/day.

20. The method of Claim 14 wherein the dosage amount is 1.0 mg/day.

21. The method of Claim 14 wherein the dosage amount is 5.0 mg/day.

22. The method of Claim 14 wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one is administered topically.

23. The method of Claim 14 wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one is administered orally.

24. The method of Claim 23 wherein the dosage amount is 0.2 mg/day.

25. The method of Claim 23 wherein the dosage amount is 1.0 mg/day.

26. The method of Claim 23 wherein the dosage amount is 5.0 mg/day.

27. The method of Claim 15 wherein the person in need of treatment does not exhibit Hamilton classification III vertex or IV male pattern baldness.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15164

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K, 31/56, 31/495, 31/50, 31/52, 31/44
US CL :514/169, 177, 253, 256, 261, 285
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/169, 177, 253, 256, 261, 285

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Registry, HCPIUS, Embrase, Biosis, Medline, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A2, 0,285,382, (MERCK AND CO., INC.) 05 October 1988, see entire document.	1-27
X	US, A, 4,377,584 (RASMUSSON ET AL.) 22 March 1983, see entire document.	1-27
X	US, A, 4,760,071 (RASMUSSON ET AL.) 26 July 1988, see entire document.	1-27
X	US, A, 5,017,568, (HOLT ET AL.) 21 May 1991, see entire document.	1-27
X -- Y	US, A, 5,155,107 (PANZERI ET AL.) 13 October 1992, see entire document.	1-11 --- 12-27
X	US, A, 5,342,948 (PANZERI ET AL.) 30 August 1994, see	1-11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 NOVEMBER 1996	Date of mailing of the international search report 02 DEC 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer REBECCA COOK Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15164

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Proceedings of the National Academy of Science, USA, issued November 1992, G. Harris et al., "Identification and selective inhibition of an isoenzyme of steroid 5 -reductase human scalp", pages 10787-10791, see entire article.	1-11
X	US, A, 5,359,071 (DURETTE ET AL.) 25 October 1994, see entire document.	1-11
X, P	US, A, 5,516,768 (HENRY) 14 May 1996, see column 8.	1-11